Hepatoprotective effect of TNFα blockade in psoriatic arthritis: A cross-sectional study

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Ann Rheum Dis published online October 22, 2009
doi: 10.1136/ard.2009.116194

ARD Online First, published on October 22, 2009 as 10.1136/ard.2009.116194

Hepatoprotective effect of TNFα blockade in psoriatic arthritis: a cross-sectional study

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Word count: 1491; word count abstract: 200

Abstract

Objective. To evaluate the impact of TNFα blockers on the presence of liver fibrosis in patients with rheumatoid arthritis (RA) and psoriatic arthritis (PsA) treated with methotrexate (MTX).

Methods. Subjects were consecutive patients with RA and PsA who had undergone MTX treatment for at least one year +/- TNF blockade for over 6 months. Liver fibrosis was assessed using non-invasive transient elastography (FibroScan). Regression models were used to compare FibroScan values of RA and PsA patients receiving TNFα blockers with those who were not.

Results. FibroScan assessments were performed on 51 RA and 43 PsA patients. Compared to RA patients, those with PsA were predominantly young males, received lower cumulative dosages of MTX and exhibited a higher incidence of liver steatosis and hyperlipidemia. An abnormal result was observed in 7.1% of the anti-TNFα-naïve and in 13% of the anti-TNFα-treated patients in the RA group, and in 30% of the anti-TNFα-naïve and 4.3% of the anti-TNFα-treated patients in the PsA group (OR = 0.11, 95% CI 0.02 to 0.98). Results of the PsA group were robust when adjusted for baseline characteristics.

Conclusion. The results suggest a protective effect of TNFα inhibitors against the development of liver fibrosis in patients with PsA.

Key words. Liver fibrosis, psoriasis, rheumatoid arthritis, methotrexate, TNFα-blocker

Longstanding treatment with methotrexate (MTX) in patients with rheumatoid arthritis (RA) or psoriatic arthritis (PsA) is associated with increased liver toxicity. Institutional guidelines for monitoring of MTX-associated hepatotoxicity are effective in most countries and include periodic determination of aminotransferase serum levels or liver biopsy (1). However, the role of liver biopsy has been questioned (2,3), and it was proposed that detection of abnormal serum levels of the aminoterminal peptide of type III procollagen might identify patients at risk, thereby reducing the number of biopsies in psoriatic patients by 45% (4). Recently, transient elastography (FibroScan) was accepted as an alternative method to quantify liver tissue stiffness (5). This method has been widely used and validated in patients with viral hepatitis where the results correlate histologically with hepatic fibrosis (6).

Anti-TNFα treatment for concomitant rheumatic disorders in patients with chronic hepatitis C (7) and non-alcoholic steatohepatitis (NASH) (8) showed a favorable outcome of the liver disease. We hypothesized that MTX-related liver toxicity could also benefit from anti-TNFα treatment, and therefore performed a prospective observational study to assess liver fibrosis using FibroScan in a population consisting of patients with PsA and RA on long-term treatment with MTX who had been started on additional TNFα-blockade.

Patients and Methods

We included RA and PsA patients with a valid baseline FibroScan (see Supplementary File 1 for detailed information) who had been consecutively recruited from the outpatient clinic of the Department of Rheumatology and Immunology at Bern University Hospital, Switzerland (see Supplementary File 2 for the patient flow).

All patients had been receiving MTX treatment for at least one year with or without anti-TNF blockade for over 6 months. RA and PsA diagnoses were based on established classification criteria (9,10). Demographic information was obtained through direct questioning (age, sex, BMI, diabetes mellitus, alcohol consumption, MTX application, folic acid supplementation) or using retrospective chart reviews (disease duration, MTX cumulative dose, hyperlipidemia, steatosis, hepatitis). Measurements of liver enzyme levels during MTX exposure were screened for any elevations (over twice the upper limit of ASAT or ALAT levels).

Analysis. Patient characteristics stratified by disease (RA and PsA) and TNFα treatment were compared using the Kruskal-Wallis rank test for continuous variables and Fisher's exact test for categorical variables. To describe the association of anti-TNFα treatments with abnormal FibroScan measurements in terms of odds ratios, we fitted logistic regression models with FibroScan assessments as the outcome variables. To assess whether the association with anti-TNFα treatment differed between RA and PsA patients we included in the regression models an appropriately constructed effect modification term and reported its p-value, allowing us to determine the statistical likelihood that effect modification was present. In sensitivity analyses we included additional baseline characteristics in the logistic regression models to adjust for BMI, age, gender, alcohol intake, diabetes mellitus, disease duration, cumulative MTX dose and cumulative folic acid dose, and tested for the interaction between each of these factors with MTX and anti-TNFα treatments. All p-values are 2-sided and analyses were performed in Stata version 10 (Stata Corporation, College Station, Texas).

Results

Patients' baseline characteristics

Table 1 demonstrates the differences in demographics, disease- and treatment-related factors, comorbidities and FibroScan findings between 51 RA and 43 PsA patients (all with oligo- or polyarticular disease courses) either treated with MTX alone or with a combination of MTX and a TNFα blocker. Compared to RA patients, those with PsA were younger and consisted of more males. PsA patients had received a lower cumulative dose of MTX with a trend to shorter disease duration compared to their RA counterparts. There was no difference between patients groups with regard to weekly MTX dose, route of MTX administration, dose of folic acid supplementation, or co-medication with non-steroidal anti-inflammatory drugs or prednisone. At the time of the FibroScan exam all patients were at least in partial remission.

When comparing the incidence of comorbidities between PsA and RA patients we found no differences in body mass index (BMI), current or past alcohol consumption, or concomitant diabetes mellitus. More patients in the PsA group had hyperlipidemia and sonographically detected liver steatosis (7 PsA *vs.* no RA patients and 7 PsA *vs.* 1 RA patient, respectively).

FibroScan measurements and association with anti-TNFα treatment

When analysing only patients with a valid FibroScan exam, we found abnormal results in 9.8% of RA patients and 16.3% of PsA patients. An abnormal result was observed in 2 of 28 anti-TNFα-naïve (7.1%) and in 3 of 23 anti-TNFα-treated (13%) patients in the RA group, but in 6 of 20 anti-TNFα-naïve (30%) and in only 1 of 23 anti-TNFα-treated (4.3%) PsA patients. When stratified by anti-TNFα treatment, these findings resulted in a crude OR of 1.95 with a 95% CI of 0.30 to 12.8 for the RA group and a crude OR of 0.11 with a 95% CI of 0.02 to 0.98 for the PsA group ($p = 0.05$ for interaction; Table 2). These findings were confirmed by the higher absolute mean FibroScan value in the anti-TNFα-naïve PsA group (8.1 kPa) compared to the other groups (FibroScan values between 4.9 and 5.5 kPA, p-value for trend 0.06; Figure 1). Our results were robust to adjustment for BMI, age, gender, alcohol intake, diabetes mellitus, disease duration, cumulative MTX dose and folic acid dose, with adjusted ORs ranging from 0.02 to 0.13 in the PsA group. When adjusting for all variables, we obtained an OR of 0.03 (95% CI 0.02 to 1.11). Adjustments in the RA group resulted in a slightly more heterogenous picture. Whereas adjustment for BMI, age, gender, alcohol intake and diabetes mellitus did not change the OR, adjustment for disease duration, cumulative MTX dose and folic acid dose yielded an adjusted OR of 1.14. However, adjusting for all variables still showed an OR of 1.73 (95% CI 0.16 to 18.2) (Table 2).

Discussion

This observational study is the first to show that treatment with TNFα blockers may exert a protective effect against liver fibrosis in patients with PsA treated with MTX. This finding was robust to the adjustment for potentially confounding factors. RA patients had lower FibroScan values than PsA patients in the MTX alone group, despite a higher cumulative dosage of MTX. These low FibroScan values may have masked a potential antifibrotic effect of TNF inhibition in the RA patient cohort. The discrepancy between the PsA and RA MTX alone groups supports earlier notions that disease-associated factors, either pathogenesis- or comorbidity-linked, play an important role in liver fibrosis.

While this is the first study that has used a mixed cohort of RA and PsA patients to report benefits of anti-TNFα treatment for liver fibrosis, it has its limitations. The number of patients was low and the duration of anti-TNFα treatment compared to MTX treatment was short. In addition, some of the data collection (e.g. disease duration, cumulative MTX dose, comorbidities) had to be done retrospectively, as we included patients with longstanding disease. However, we tried to minimize the impact of this potential bias by blinding the chart reviewer to the FibroScan outcome.

Our results are in good agreement with the favorable hepatological outcomes previously described in patients with chronic hepatitis C (7) or NASH (8) following anti-TNFα treatment for concomitant rheumatic disorders. These human data, as well as recent results obtained from an experimental model of NASH in the rat (12), underline the pathogenic role of TNFα in acute and chronic liver disorders. There is an abundance of indirect evidence that TNFα might be involved in the pathogenesis of liver fibrosis in systemic rheumatic diseases caused either by the inflammatory rheumatic processes themselves or by concomitant comorbidities. For instance, TNFα plays a key role inducing fibrogenic growth factors such as transforming growth factor beta (TGFβ) (13) and connective tissue growth factor (CTGF) (14) in fibrotic liver diseases. Additionally, liver fibrosis is thought to be the result of chronic portal inflammation in non-alcoholic fatty liver disease (15) that is often linked to obesity (16) and dyslipidemia (17), comorbidities that along with diabetes mellitus define the metabolic syndrome that is often associated with psoriasis (18). Moreover, patients with MTX-treated psoriasis and risk factors for liver disease, particularly type 2 diabetes or obesity, are at higher risk of developing severe liver fibrosis compared to those without such risk factors, even when lower cumulative MTX doses are given (19). Accordingly, in our study we found a higher prevalence of liver steatosis and dyslipidemia at baseline in the PsA group compared to the RA group.

We cannot discern whether the higher frequency of liver pathology in PsA patients is due to associated hepatotoxic comorbidities such as liver steatosis rather than to liver disease caused by the chronic immunologically mediated inflammatory process itself. Irrespective of the cause of liver inflammation, however, the results of this study provide the first evidence that anti-TNFα treatment is likely to protect against the evolution of liver fibrosis in PsA patients. To validate the findings of our study, prospective studies with repeated FibroScans in PsA patients before and after starting MTX and/or anti-TNFα treatment will be needed.

Competing interests: None declared
Ethics approval: The local research committee deemed the study as a quality improvement activity and waived the requirement for institutional review board approval.
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Figure Legends

Figure 1. FibroScan measurements expressed in kPa. Data on patients belonging to each disease and treatment group are expressed as means of values with a 95% confidence interval.

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Table 1. Patients' baseline characteristics

	Rheumatoid Arthritis		Psoriatic Arthritis		p-value
	TNF – (n=28)	**TNF + (n=23)**	**TNF – (n=20)**	**TNF + (n=23)**	
Age [years, SD]	60.3 (9.2)	57.0 (12.5)	51.9 (14.1)	51.3 (10.9)	0.02
Females [numbers, %]	16 (57.1)	17 (73.9)	6 (30.0)	7 (30.4)	0.006
BMI [kg/m^2, SD]	26.0 (3.8)	25.4 (4.4)	26.4 (3.8)	27.0 (4.5)	0.60
Disease duration (years, SD)	17.3 (10.8)	13.0 (11.2)	9.5 (7.6)	11.8 (11.2)	0.07
MTX dose per week (mg, SD)	16.4 (3.8)	16.0 (3.3)	16.1 (4.6)	15.4 (5.4)	0.87
MTX cumulative dose (g, SD)	6.9 (5.4)	3.8 (3.2)	2.7 (2.3)	3.7 (3.2)	0.001
Folic acid cumulative dose (g, SD)	11.8 (3.5)	9.7 (4.4)	9.8 (5.0)	9.4 (3.0)	0.11
Diabetes mellitus [numbers, %]	2 (7.1)	1 (4.3)	3 (15.0)	3 (13.0)	0.64
Steatohepatitis [numbers, %]	0 (0.0)	1 (4.3)	4 (20.0)	3 (13.0)	0.05
Hyperlipidemia [numbers, %]	0 (0.0)	0 (0.0)	4 (20.0)	3 (13.0)	0.009
Any alcohol consumption [numbers, %]	4 (14.3)	3 (13.0)	7 (35.0)	5 (21.7)	0.28
Daily alcohol consumption (g, SD)	4.3 (12.8)	4.6 (12.3)	11.3 (16.6)	4.3 (10.4)	0.24
Elevated liver enzymes [numbers, %]	3 (10.7)	9 (39.1)	7 (35.0)	10 (43.5)	0.10

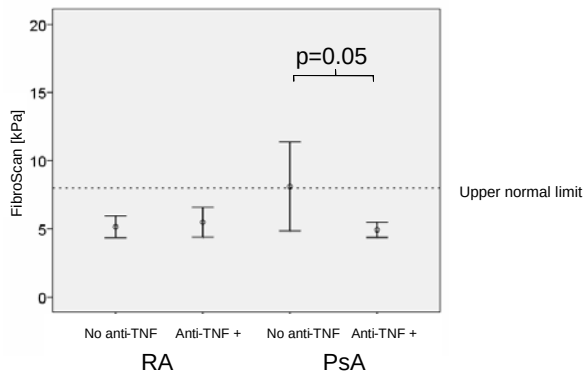
Baseline characteristics of the 94 patients with rheumatoid arthritis and psoriatic arthritis, treated with (TNF+) or without (TNF-) TNFα blockers, are presented as means with standard deviations or numbers with percentages. P-values are derived using the Kruskal-Wallis rank test for continuous variables and the Fisher's exact test for categorical variables.

Table 2. Association of pathologic FibroScan measurements with anti-TNFα treatment in RA and PsA patients

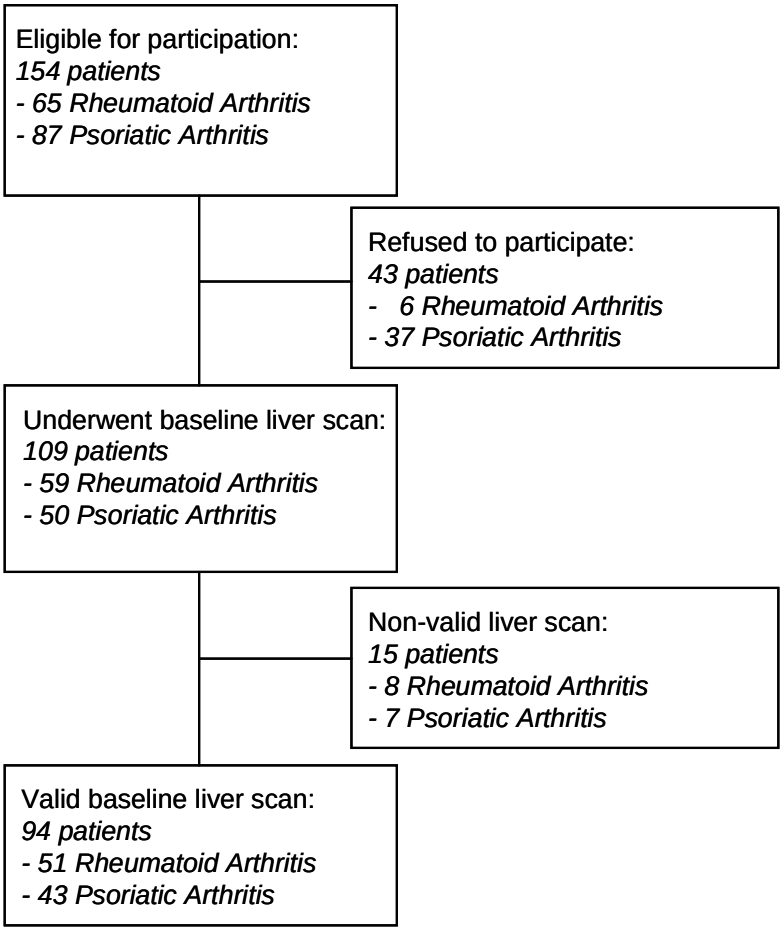
variable adjustment	RA (n=51) OR*, 95% CI	PsA (n=43) OR*, 95% CI	p-value for interaction**
crude	1.95 (0.30 to 12.8)	0.11 (0.02 to 0.98)	0.05
adjusted for BMI, age, gender	1.93 (0.27 to 13.7)	0.03 (0.002 to 0.64)	0.03
adjusted for alcohol intake	1.94 (0.29 to 13.0)	0.13 (0.08 to 1.25)	0.055
adjusted for diabetes mellitus	1.89 (0.29 to 12.5)	0.10 (0.01 to 0.97)	0.048
adjusted for disease duration, cumulative MTX dose and folic acid dose	1.14 (0.14 to 9.13)	0.02 (<0.01 to 0.61)	0.077
adjusted for all variables	1.73 (0.16 to 18.2)	0.03 (0.001 to 1.11)	0.063

* OR=odds ratios

** p - values and 95% confidence intervals (CI) are derived from logistic regression models.



Supplementary File 2



Patient Flow chart

Sixty-five RA and 87 PsA patients from the outpatient clinic of the Department of Rheumatology and Clinical Immunology & Allergology at the University Hospital of Bern, Switzerland, were asked to participate in this observational study. Six RA patients and 37 PsA patients refused to participate. A total of 109 patients (59 with RA and 50 with PsA) were referred to the Institute of Clinical Pharmacology at Bern University Hospital, Switzerland, in order to undergo a transient elastography (FibroScan) exam. Of this population, 8 RA and 7 PsA patients had invalid FibroScan measurements for technical reasons. Valid baseline FibroScan results were obtained from 51 RA and 43 PsA patients.